	Folfox 3: 24 pts	Folfox 4 20 pts	All: 44 pts
Pts (PR/SD/PD)	5/9/10	7/4/9	12/13/19
RR% [CI]	21 [7 1–42.1]	35 [15 3–59.2]	27 [14.9–42.7]

These preliminary results confirm previous reports of L-OHP preclinical and clinical synergy with 5FU in 5FU resistant MCRC. A new study with L-OHP at 100 mg/sqm is planned to elucidate eventual LOHP dose-response relationship.

739 POSTER

The value of postoperative surveillance after radical surgery for colorectal cancer

M. Daniels[1], X. Bessa, A. Castells, S. Albiol[1], N. Viñolas[1], J.M. Piqué, J. Terés, J. Estapé[1]. *[1]Oncology; Gastroenterology Departments, Hospital Clinic, University of Barcelona, Barcelona, Spain*

Purpose: Early detection of recurrence after curative resection for primary colorectal cancer (CRC) should improve patients' (pts) prognosis. The present cohort study was aimed at assessing the effectiveness of systematic follow-up in pts with CRC, both regarding the rate of tumour recurrence amenable to curative-intent surgery and survival.

Methods: Between July'87 and June'90, 199 CRC pts who underwent radical surgery were followed according a previously well-defined post-operative surveillance programme which consisted on laboratory studies (including serum CEA assay) every 3 months, physical examination and abdominal ultrasound or computed tomography every 6 months, and chest radiograph and total colonoscopy once a year. Cohorts were defined according patients' compliance to the follow-up protocol.

Results: One hundred forty pts (70%) were considered to be compliant with the surveillance programme (cohort A), while the remaining 59 pts occasionally attended follow-up investigations (cohort B), both cohorts being similar with regards baseline characteristics. Although there were no differences in the overall recurrence rate (38% vs 41%; ns), curative-intent reoperation was possible in 18 pts (34%) of those with tumour recurrence in the cohort A, but in only 3 pts (12%) in the cohort B ($p = 0.05$). Similarly, the probability of survival was higher in the cohort A, both regarding overall (63% vs 37% at 5 years; $p < 0.001$) and CRC-related (69% vs 49% at 5 years; $p < 0.02$) rates. Cox regression analysis disclosed that only a more advanced Dukes' stage (OR: 8.17, 95%CI: 1.13–59.29) and non compliance with the postoperative surveillance programme (OR: 2.32, 95%CI: 1.50–3.60) had an independent negative impact on survival.

Conclusions: Systematic postoperative surveillance in pts with CRC operated on for cure increases both the rate of tumour recurrence amenable to curative-intent surgery and survival.

740 POSTER

Significance of matrix metalloproteinase 9 (MMP-9) and matrix metalloproteinase 3 (MMP-3) expression during liver metastasis in colorectal cancer

K. Inuzuka, Y. Ogata, A. Ohkita, J. Konishi, H. Oda, Y. Harada, Y. Hara, M. Kanazawa, K. Shirouzu. *Department of Surgery, Kurume University School of Medicine, Japan*

Purpose: Degradation of extracellular matrix is considered to be essential process for tumor invasion and metastasis. Activities of matrix metalloproteinases (MMPs) which has a capability of degradation of all matrix components are regulated by activators and inhibitors such as tissue inhibitors of metalloproteinases (TIMPs). Our previous study showed that pro MMP-9 was activated by MMP-3 directly. To clarify clinical significance of MMP-9 and MMP-3 expression in colorectal cancer, we have studied MMP-9 and MMP-3 expression immunohistochemically.

Methods: Paraffin embedded spicemens from 194 patients with colorectal cancer who were underwent operation between 1988 and 1991 were immunostained for MMP-9 and MMP-3.

Results: MMP-3 was localized only in stromal cells such as monocyte, macrophages, whereas MMP-9 was noted in both tumor cells and stroma. The incidence of MMP-9 expression in the tumor cells was 39.7% and that of MMP-3 in the stroma was 22.2%. There were strong relationship between liver metastersis and the expression of MMP-9 and/or MMP-3. In interest colon, both enzymes significantly coexpressed.

Conclusion: MMP-9 and MMP-3 may play an important role in liver metastasis and tumor invasion. In particular, MMP-3 may act as an activator for proMMP-9.

741 POSTER

The identification of high risk patients with metastatic colorectal cancer

T. Sahmoud, E. Grabowska, G. Blijham, C.H Köhne, M.L. Couvreur, D. Curran, J. Wils. *EORTC Data Center, Belgium*

Purpose: Identification of prognostic factors in metastatic colorectal cancer.

Methods: Four hundred and seventy seven previously untreated patients (pts) who were randomized in two consecutive phase III trials of the EORTC Gastrointestinal Tract Cancer Cooperative Group (high-dose 5-FU (HD-5FU) ± low-dose methotrexate (LD-MTX) and HD-5FU/LD-MTX ± LD-PALA) were included in the analysis. The Cox model was used for the analysis.

Results: The median duration of survival for all patients was 12 months. Prolonged survival was observed for patients who had a longer duration since first diagnosis ($p = 0.001$), rectum as the primary tumor site ($p = 0.035$), good performance status ($p < 0.001$), none or little weight loss ($p < 0.001$), initial white blood cells $\leq 8 \times 10^9/l$ ($p < 0.001$), initial granulocyte count $\leq 5 \times 10^9/l$ ($p < 0.001$), initial platelet count $\leq 350 \times 10^9/l$ ($p < 0.001$), normal hemoglobin level ($p = 0.001$), normal serum bilirubin ($p = 0.021$) and normal alkaline phosphatase ($p < 0.001$). The multivariate model retained the following factors of poor prognosis: thrombocytosis ($p < 0.001$), weight loss ($p < 0.001$), abnormal serum bilirubin level ($p < 0.001$) and granulocytosis ($p < 0.001$). There was evidence that the effect of the initial granulocyte count on survival was more prominent during the first year.

Conclusion: Some biological variables are important prognostic factors for survival in patients with metastatic colorectal cancer. These factors should be taken into consideration in the design of new trials.

742 POSTER

Sphincter-saving operations for cancer localised in the distal half of the rectum

V. Dimitrov, Ts. Loukanov, Kr. Ralchev, P. Kurtev, Zl. Dudunkov. *National Center of Oncology, Sofia, Bulgaria*

Purpose: The goal of this prospective study is to present the broad use of the sphincter saving operations for treatment of rectal cancer, localised in the distal half of the rectum.

Materials and Methods: In order to determine the usefulness of sphincter – saving operations were analysed 784 patients operated radically on rectum cancer at the Dept. of Surgery in NCO for the period from 1.1.1984 to 31.12.1996. Discussed are the techniques, clinical observations and post-operative results in the seven most widely used in our clinic sphincter-saving operations.

Results: The authors emphasised upon the very low percent of the local recurrences for 5 years follow up 5.3 ± 1.1%. This is one of the lowest percent of local recurrences after sphincter-saving operations of the rectum for cancer in the literature. Discussed are the indications for bilateral lymphatic dissection and for excluding the bowel passage with transversostomy. The anal continence was satisfactory in all of the applied methods (proved tonometrically).

Conclusion: The methods introduced in our clinic for cancer treatment in the distal rectum half not only increased the number of the sphincter-saving operations, but decreased considerably the postoperative complications. All this give us a guarantee not only to continue to apply them, but to propose them for broader application in the everyday practice.

743 POSTER

Treatment of liver metastases and moderate peritoneal carcinomatosis by hepatectomy and cytoreductive surgery followed by immediate postoperative chemotherapy: Feasibility and preliminary results

P. Dubé, D. Elias, S. Bonvalot, P. Meshka, M. Manai, A. Cavalcanti, M. Ducreux, Ph. Lasser. *Departement de chirurgie et de gastro-entérologie, Gustave-Roussy Institute, Villejuif, France*

The purpose of this study is to report tolerance, and preliminary results in patients with liver metastases synchronous to moderate peritoneal carcinomatosis, treated with a hepatectomy and complete cytoreductive surgery, immediately followed by postoperative intraperitoneal chemotherapy. Twleve patients with liver metastases, and moderate pertioneal carcinomatosis were included in the study. They all had liver resection for metastases, complete cytoreductive surgery of the peritoneal carcinomatosis, and immediate

intraperitoneal chemotherapy. Mean operative times was 323 minutes, and mean blood loss were 1 207 milliliters. There was no mortality. Morbidity was related to four transient biliary leakages. There was no systemic complication due to chemotherapy. Hospital stay was 22 days. After a median follow-up of 14.4 months, there was no detectable recurrence of the peritoneal carcinomatosis. At the end of the study, seven patients were disease free. When minimal or moderate peritoneal carcinomatosis is detected during hepatic metastasectomy, the association of a hepatectomy with complete cytoreductive surgery of peritoneal carcinomatosis immediately followed by intraperitoneal postoperative chemotherapy is logical, and safe. This agressive treatment is well tolerated, although the frequency of biliary leakages is higher than after standard hepatectomy. Absence of peritoneal recurrence, and rate of survival are promising.

744 POSTER

Biological factors predicting the outcome of regional chemotherapy in colorectal carcinoma metastases to liver

J. Zaloudik, V. Vagunda, M. Drahokoupilová, L. Janáková, J. Kalabis, M. Nekulová, B. Vojtešek, I. Kocák, P. Karásek. *Masaryk Memorial Cancer Institute, Brno, Czech Republic*

Purpose: Regional intrahepatic chemotherapy may be beneficial for selected subgroup of patients with liver metastases of colorectal carcinoma. However, biological criteria precising indications to this demanding type of treatment have not yet been established.

Methods: Twenty two cases of colorectal carcinoma metastases to liver treated by regional chemotherapy were analysed for DNA ploidy and PCNA, Ki67, p53, p21 (WAF1), mdm2, c-erb2, CEA, CA19-9 and P-glycoprotein (MDR) expression and results related to survival.

Results: Mean survival of patients with DNA diploid tumors was significantly longer (20 versus 11 months, P = 0.04) comparing to DNA aneuploid ones. Only the trend for lower PCNA positivity and p53 expression could be observed among DNA diploid tumors. All p53 positive cases were negative for p21 (WAF1) and mdm2. Other parameters were unrelated to outcome of treatment.

Conclusion: DNA ploidy, perhaps together with p53 overexpression and PCNA positivity, may be predictive of effectiveness of regional intrahepatic chemotherapy performed for colorectal cancer liver metastases. However, a larger study is needed to confirm these preliminary findings. (Supported by IGA MZ CR grant No.2923-3)

745 POSTER

Infusional 5-fluorouracil with and without calcium-folinat as second line therapy in advanced colorectal cancer – A retrospective cohort study of different protracted infusion regimens

F. Gutzler, M. Moehler, M.W.J. Boehme, E. Will, U. Raeth, W. Stremmel. *Department of Internal Medicine GI-Unit, University Hospital of Heidelberg, Germany*

Purpose: Biomodulation of 5-Fluorouracil (5-FU) with Calciumfolinat (CF) in bolus regimens increases response rates, and probably survival rates of patients with advanced colorectal cancer (CRC). The benefit of CF in second line protracted infusional protocols of 5-FU is not so clearly defined. Consequently we compared the outcome of two infusional 5-FU regimens with and without CF.

Methods: Fifty-eight patients with CRC were treated from May 1991 until September 1996 with two different second line infusional 5-FU protocols after failure of CF-modulated 5-FU – bolus regimens (380–450 mg/m^2 5-FU + 20–200 mg/m^2 CF d1–5 q 4w). Twenty-eight patients received 60 mg/kg 5-FU alone as a 48 hours infusion with ambulatory pumps every week until progression. Thirty patients were treated with 500 mg/m^2 CF as a 2 hours infusion followed by 2600 mg/m^2 5-FU as a 24 hours infusion every week with a third weeks rest until progression. Kaplan-Meier survival analysis and the log-rank-test were applied.

Results: The two cohorts were adequately matched in respect of age, tumor load, and time to progression after first line therapy, and received a mean of 27 resp. 14 cycles. The CF-scheme exhibits higher response rates but more toxicity. Median survival times (30 resp. 46 months) were significantly different (p = 0.09).

Conclusions: CF modulation of 5-FU in protracted infusional protocols as second line therapy increases response rates and survival rates of CRC patients.

746 POSTER

Oxaliplatin (LOHP) and 5-fluorouracil (5-FU) synergism in advanced colorectal cancer patients (ACRC)

V. Meyer[2], R. Delva[1], E. Gamelin[1], B. Lamezec[1], P. Maillart[1], E. Danquechin-Dorval[3], A. Lortholary[1], M. Boisdron-Celle[1], M. Maigre[4], S. Brienza[5], E. Cvitkovic[6], F. Larra[1]. [1]*C.R.L.C.C. Papin;* [2]*C.H.U., Angers;* [3]*CHU, Clinique Fleming, Tours;* [4]*CH Saumur;* [6]*C.H.U. Paul Brousse, Villejuif;* [5]*Debiopharm, Charenton, France*

Previous in vitro and in vivo studies reported LOHP and 5-FU synergistic effect in ACRC. We studied their combination in 5-FU refractory ACRC. **Pts and Methods:** pts had high dose 5-FU-folinic acid (FA) refractory ACRC (progressive disease while on 5-FU-LV treatment). LOHP was added, at 130 mg/m^2/3 weeks by IV infusion over 2 hours, to unchanged 5FU-LV schedule, 1.3 g/m^2 weekly 5-FU, plus 400 mg/m^2 FA.

Results: 38 patients from 6/94 to 5/96, with measurable disease in all pts. Mean age: 64; PS: 0 (15), 1 (15), 2 (7), 3 (1), sites involved: liver: 27, lung: 7, peritoneum carcinomatosis with measurable mass: 10, lymphnode: 1, number of sites involved: 1 site: 26, 2 sites or more: 12; previous radiotherapy: 9; mean duration of 5-FU-LV-LOHP: 4 cycles (1 to 12). WHO toxicity was: neuropathy: 56 GI, 15 GII, in 22 pts; neutropenia: 10 GI, 4 GII, 2 GIII in 7 pts; thrombopenia: 8 GI, 6 GII, 4 GIII in 8 pts; diarrhea 15 GI, 18 GII, 6 GIII in 14 pts; 8 pts (21%) had grade III toxicity. Responses (WHO): 14 PR (36%), 14 SD, and 10 PD after 3 cycles of LOHP-based treatment; mean duration of the response: 6 mths (1 to 11), median Progression Free Survival: 5.5 mths, median Overall Survival: 7.6 mths, 9 pts were alive at +12 mths.

Discussion: LOHP-5-FU-LV have synergistic activity; toxicity is mild; response rate appears to be higher than expected with LOHP alone in 5-FU refractory ACRC. This combination merits further investigation in first line chemotherapy.

747 POSTER

Biweekly administration of methotrexate (MTX), levofolinic acid (LFA), and 5-fluorouracil (5-FU) in advanced colorectal carcinomas

R. Casaretti, P. Comella, G. Cartenì, L. Manzione, M. Biglietto, L. De Lucia, A. Daponte, A. Gallipoli, F. Caponigro, V. Lorusso, G. Palmieri, A. Gravina, G. Comella. *Gruppo Oncologico Campano c/o Natl. Tumor Inst. of Naples, Italy*

Background: In a previous phase II study, 54 colorectal cancer patients (pts) received biweekly MTX (500 mg/m^2) 24 h before 5-FU (600 mg/m^2) + LFA (250 mg/m^2) administration. A 26% ORR was observed in chemo-naive pts.

Purpose: To test whether higher MTX and 5-FU doses could improve the ORR without increasing the acute toxicity.

Methods: Patients with advanced colorectal cancer received MTX 750 mg/m^2 on d 1 followed 24 h later by 5-FU 800 mg/sqm and LFA 250 mg/m^2 every 2 weeks until PD or for a maximun of 16 courses.

Results: As of Jan 97, 100 pts were enrolled and 90 pts (48 chemo-naive, 42 pretreated) were evaluable for response (10 pts were too early), according to intention-to-treat analysis. Overall, 25 pts achieved a response: 19/48 (40%, 95%CI = 26–55) chemo-naive and 6/42 (14%, 95%CI = 5–29) pretreated pts. Toxicity: the treatment was usually well tolerated, but 3 treatment-related deaths and 4 early withdrawals for toxicity occurred. Only 2/7 of these events were observed in chemo-naive pts. Grade 3–4 mucositis and diarrhoea occurred in 12% and 9% of courses, respectively, and were less frequent in chemo-naive pts. Grade 4 neutropenia and thrombocytopenia each occurred in less than 5% of courses.

Conclusions: The biweekly administration of MTX followed by 5-FU+LFA is a well tolerated treatment for colorectal cancer pts and it shows a very interesting activity both in chemo-naive and pretreated pts.

748 POSTER

Insulin-like growth factor binding protein-3 (IGFBP-3) proteolysis in patients with colorectal cancer: A possible early prognostic factor of metastatic progression

M. Bacluchka[1], M. Remacle-Bonnet[2], F. Garrouste[2], B. Sastre[3], R. Favre[1], G. Pommier[2]. [1]*Oncologie Médicale, CHU Timone;* [2]*URA CNRS 1924, Faculté de Médecine;* [3]*Chirurgie Digestive, Hôpital Ste Marguerite, Marseille, France*

Purpose: The Insulin-like Growth Factor (IGF) system plays a key role in intestinal epithelial cell functions and colorectal neoplastic growth. In human,